Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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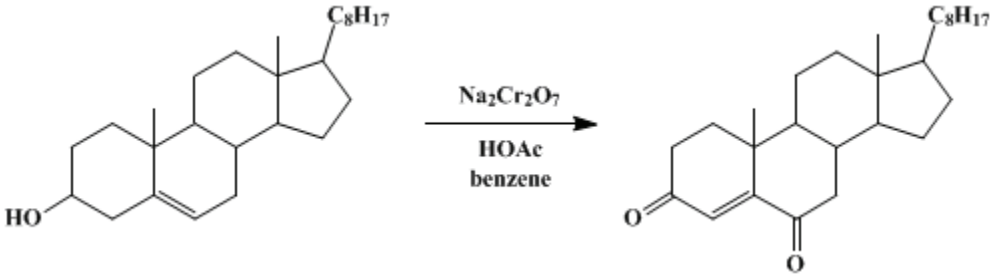
Δ⁴-CHOLESTEN-3,6-DIONE

[Cholest-4-ene-3,6-dione]



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1. Procedure

A 500-ml. Erlenmeyer flask containing 64 g. (10 oxygen equivalents) of sodium dichromate dihydrate and 225 ml. of acetic acid is heated and swirled until all the solid has dissolved, and then is cooled in an ice bath to bring the temperature of the solution to 15°. In a 1-l. Erlenmeyer flask 25 g. (0.065 mole) of commercial cholesterol is dissolved in 225 ml. of benzene by brief warming, and the solution is cooled to 20°; 225 ml. of acetic acid is added, the solution is cooled to 15°, and the dichromate solution (at 15°) is poured in, whereupon a thick orange paste of cholesteryl chromate, $(C_{27}H_{45}O)_2CrO_2$, separates. The flask is immersed in an ice-water bath that is allowed to stand in a refrigerator for 40–48 hours. No stirring or other attention is required in this period; the temperature soon drops to 0° (Note 1), and the chromate dissolves in a few hours.

The resulting brown solution is poured into a separatory funnel and shaken with 225 ml. of 30–60° petroleum ether. After brief standing, the mixture when viewed against a strong light can be seen to have separated into a reddish upper hydrocarbon layer and a smaller, very dark lower layer containing chromium compounds and acetic acid. The lower layer is drawn off and discarded. Then 50 ml. of water is added to the hydrocarbon layer, and the mixture is shaken and allowed to settle. Another lighter-colored, lower layer is drawn off and discarded, and the process is repeated with 50 ml. more water. The hydrocarbon layer, now light in color, is then shaken with 110 ml. of Claisen's alkali (Note 2); this first portion neutralizes the residual acetic acid and acidic oxidation products and extracts some of the enedione as the yellow enolate. The funnel is allowed to stand, with occasional twirling, until the lower layer has settled to a clear yellow solution; the upper hydrocarbon layer acquires a dirty red-brown color. The extract is drawn off into a wide-mouthed 2-l. separatory funnel charged with 200 ml. of water, 600 g. of ice, 200 ml. of 36% hydrochloric acid, and 300 ml. of ether (Note 3). The hydrocarbon layer is extracted in the same way with five more 100-ml. portions of Claisen's alkali and then discarded (Note 4).

After the last alkaline extract has been run into the receiving funnel, this is shaken and the aqueous layer is drawn off and discarded. The light-yellow ethereal layer is run into a smaller funnel and shaken with 100 ml. of 5% sodium carbonate solution and 30 ml. of saturated sodium chloride solution (Note 5). This extraction is repeated a second time (Note 6). The carbonate extract is either discarded or worked up for recovery of acidic oxidation products (Note 7). The ethereal solution is finally shaken with 100 ml. of saturated sodium chloride solution, filtered into a round-bottomed flask (Note 8) by gravity through a paper containing 25 g. of anhydrous magnesium sulfate, and evaporated to dryness. The residue is initially an oil, but when the last traces of solvent are removed by evacuating the flask (Note 8), reheating, and re-evacuating, it is obtained as a yellow solid (about 13 g.). This is taken up in 125 ml. of boiling methanol, and crystallization is allowed to proceed, first at room temperature and then at 0°. Δ⁴-Cholesten-3,6-dione separates in glistening, thin, yellow plates, m.p. 124–125°; yield in the first crop, 9.0–9.3 g. Concentration of the filtrate affords a second crop of 0.7–1.2 g., melting in the

range 118–121.5°; total yield, 10.0–10.2 g. (39–40%).

2. Notes

1. The temperature of the oxidation is highly critical. When the mixture, initially at 15°, is allowed to stand in a refrigerator at an air temperature of 4–8°, the temperature of the reaction mixture during the first 7 hours is in the range 18–5° (exothermic); yields of enedione after varying reaction periods are as follows: 7 hours, 27%; 15–22 hours, 32.5% (less-pure product). At 25° the enedione is oxidized completely to acids in about 18 hours.
2. Sufficient Claisen's alkali for one run is made by dissolving 175 g. of potassium hydroxide pellets in 125 ml. of distilled water, cooling to room temperature, adding 500 ml. of methanol, and again cooling; this gives 655–665 ml. of solution.
3. Δ^4-Cholesten-3,6-dione is sensitive to air oxidation under certain conditions, particularly in alkaline solution. If the protective procedure specified is not followed the reaction product may be deep red and tarry.
4. The residual solution contains a little cholesterol, 0.2–0.3 g. of Δ^4-cholesten-3,6-dione, and small amounts of products derived from the oxidation of cholestanol and other companions.
5. Sodium chloride speeds up the separation of layers.
6. The sodium carbonate extract contains only a few milligrams of the enedione.
7. The oxidation procedure described affords a mixture of acids from which no component is easily isolable. When the oxidation is allowed to proceed in the temperature range 18-5° for 15–22 hours, as described in (Note 1), isolation of the Diels acid (3,4-seco-Δ^5-cholesten-3,4-dioic acid) is easily accomplished as follows. The carbonate extract is acidified and shaken with ether, and the clear aqueous layer is discarded. The ethereal solution, which may contain some suspended Diels acid, is not dried but is run into a flask and diluted with an equal volume of acetone. The mixture is evaporated to a volume of 15–20 ml. and cooled, and the Diels acid is collected as a white powder, m.p. 280–285°; yield 0.5 g.
8. A round-bottomed flask is recommended in order to withstand the evacuation process.

3. Discussion

Mauthner and Suida[2] isolated, as one of three neutral products resulting from the oxidation of cholesterol with aqueous chromic acid in acetic acid solution, the substance later identified as Δ^4-cholesten-3,6-dione. The present procedure is based upon results of a reinvestigation of the oxidation by a low-temperature, non-aqueous procedure.[3]

References and Notes

1. Harvard University, Cambridge 38, Massachusetts.
2. Mauthner and Suida, *Monatsh.*, **17**, 579 (1896); Windaus, *Ber.*, **39**, 2249 (1906); Ross, *J. Chem. Soc.*, **1946**, 737.
3. Fieser, *J. Am. Chem. Soc.*, **75**, 4386 (1953).

Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

petroleum ether

Δ^4-Cholesten-3,6-dione

3,4-seco-Δ^5-cholesten-3,4-dioic acid

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

oxygen (7782-44-7)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

chromic acid (7738-94-5)

magnesium sulfate (7487-88-9)

cholestanol (80-97-7)

Cholesterol (57-88-5)

sodium dichromate dihydrate (10588-01-9)

cholesten-3,6-dione

Cholest-4-ene-3,6-dione (984-84-9)

cholesteryl chromate